PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Wells *et al.*

Serial No.: 09/691,237

Filed: October 19, 2000

For: SUSTAINED-RELEASE FORMULATIONS FOR TREATING CNS-MEDIATED DISORDERS

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DECLARATION

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Sir:

I, David S. Wells, say that:

(1) I, David S. Wells, a coinventor of the above-referenced patent application, am a citizen of the United States currently residing at 127 F Street, Salt Lake City, UT 84103. I received a Ph.D. in Toxicology from the State University of North Carolina in 1985. I have been employed at NPS Pharmaceuticals, Inc. ("NPS") since 1996 and am currently Senior Director of Pharmacokinetics, Drug Metabolism, and Safety Assessment. NPS is the

assignee of record of the above-referenced patent application. I have worked in the pharmaceutical industry since 1985. Before my employment at NPS, I was employed at Wyeth Laboratories (Radnor, PA) and Rhône-Poulenc Rorer (Collegeville, PA), now Sanofi-Aventis. I have spent my 20-year pharmaceutical career working in the field of pharmacokinetics and drug metabolism. During this time, I have worked with a variety of pharmaceutical chemists on the development of prototype formulations for the successful delivery of new chemical entities. These included the controlled-release of an adenosine agonist, the controlled release of a GLP-2 analog, the controlled-release of isovaleramide, the transdermal-permeation of calcitonin, the transdermal permeation of parathyroid hormone, and the intranasal delivery of triamcinolone.

(2) In connection with the captioned application, I have reviewed, and believe that I understand, those portions of the Office Action mailed April 1, 2005, that relate to U.S. Patent No. 4,571,333 to Hsiao *et al.* ("Hsiao") and WO 99/44623 to Artman *et al.* ("Artman"), which are cited in the above-referenced Office Action.

(3) I have read the claims of the above-referenced patent application, as exemplified by independent claims 35, 48, and 51 as amended in response to the Office Action mailed April 1, 2005.

(4) The invention claimed in the above-referenced patent application is based on my and the coinventors' recognition that isovaleramide has a short half-life *in vivo*. The short *in vivo* half-life was discovered by me and the coinventors in 1998, during NPS' first human clinical trial of isovaleramide. From the results obtained in this clinical trial, I calculated the mean plasma clearance of isovaleramide to be approximately 3 ml/minute/kg body weight and the mean plasma half-life of isovaleramide to be approximately 2.5 hours.

(5) It is presently believed that doses of 1200 to 3600 mg/day will provide therapeutically effective plasma concentrations of isovaleramide. However, with a half-life of 2.5 hours,

dosing between 1200 to 3600 mg of isovaleramide per day using an immediate release formulation would result in large differences in peak to trough plasma concentrations. For example, a 2400 mg daily dose (administered as 1200 mg every 12 hours) delivered using an immediate release formulation would result in a mean peak plasma concentration of 27.6 μg/ml, which would decline to a trough concentration of 1.18 μg/ml just prior to the next dose 12 hours later. This 23-fold change in concentration over the dosing period would potentially subject patients to peak concentrations that are undesirably high and trough concentrations that may be subtherapeutic, an unacceptable condition in the treatment of a life-threatening disease, such as epilepsy. In light of the short half-life and predicted dosing range, the coinventors and I recognized the desirability of a sustained release formulation of isovaleramide, which would provide a smaller peak to trough plasma concentration range.

(6) The short half-life of isovaleramide was not predicted and would not have been appreciated without the human clinical trial conducted by NPS in 1988. In this case, hepatocyte metabolism experiments, which are considered to be traditional *in vitro* prediction tools, resulted in a very low level of isovaleramide biotransformation and, thus, did not allow accurate prediction of the *in vivo* half-life results. Therefore, without having the data from the first human clinical trial, the half-life of isovaleramide in humans would have been predicted to be much longer than the half-life actually determined during the human clinical trial. Based on this erroneous prediction of the *in-vivo* half-life of isovaleramide, such large differences in peak to trough plasma concentrations were not expected and the desirability of a sustained release formulation of isovaleramide would not have been appreciated.

(7) Hsiao states that "different types of controlled release oral dosage forms have been developed, but each has disadvantages which affect its suitability to a particular drug." Hsiao at column 3, lines 6-9. Hsiao also states that "[w]ide variations in the physico-chemical and pharmacokinetic properties of different drugs impose such varied

requirements on the design of controlled drug delivery formulations, that formulations that are suitable for one drug cannot generally be predictably applied to other drugs." *Id.* at column 3, lines 9-14. Therefore, as described in Hsiao, the development of a sustained-release composition for a given active compound is a complicated and expensive process. Additionally, providing the active compound in a sustained-release composition can increase the difficulty and costs of the manufacturing process. These statements in Hsiao reflect an understanding, endemic to the field of pharmacokinetics and drug metabolism, that the components of a sustained-release formulation of one active compound will not necessarily provide effective sustained-release of a different active compound.

(8) A person of ordinary skill in the art, working in this field, would not formulate a given active compound into a sustained-release composition without a clinical reason for doing so. This is particularly true in the case of isovaleramide, isovaleric acid, or the related compounds recited in the claims of the above-referenced patent application. Furthermore, a person of ordinary skill in the art would not have expected that adding HPMC as taught in Hsiao's sustained-release naproxen composition to the compositions of Artman would produce a composition that provides sustained-release of an active compound as taught and claimed in the above-referenced patent application.

(9) Prior to our invention and to the disclosure in the above-referenced patent application, a person of ordinary skill in the art would not have undertaken the effort and expense to provide isovaleramide, isovaleric acid, or the related compounds recited in the claims of the above-referenced patent application in a sustained-release composition. In other words, a person of ordinary skill in the art in the field of pharmacokinetics and drug metabolism would not have been motivated, based on the teachings of Artman and Hsiao, to formulate isovaleramide, isovaleric acid, or the other compounds recited in the claims into a sustained-release composition.

(10) The claims in the above-referenced patent application recite "an oral sustained-release composition" wherein the amount of active compound ranges from "about 40% to 70% by weight" of the composition. Hsiao teaches a sustained-release naproxen composition that contains from 81-96% by weight naproxen, a formulation that is unlikely to be successful in delivering isovaleramide at doses up to 3600 mg/day. Hsiao makes no mention of a sustained-release composition that contains a smaller amount of any active compound. Artman is the only cited reference that relates to isovaleramide compositions. However, Artman does not teach sustained-release compositions, let alone sustained-release compositions that comprise from about 40% to 70% by weight of the active compound. Thus, a person of ordinary skill in the art would not find any guidance in Artman and Hsiao that would lead to the production of the claimed oral sustained-release pharmaceutical compositions, which comprise from about 40%-70% by weight of the active compound.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

David S. Wells

29 SEP 2005

Date

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